REVIEW

Diaphragm-protective mechanical ventilation in acute respiratory failure

Taiga Itagaki

Department of Emergency and Disaster Medicine, Tokushima University Hospital, Tokushima, Japan

Abstract : Mechanical ventilation injures not only the lungs but also the diaphragm, resulting in dysfunction associated with poor outcomes. The chief mechanisms of ventilator-induced diaphragm dysfunction are : disuse atrophy due to insufficient contraction and excessive ventilatory support ; concentric load-induced injury due to excessive contraction and insufficient ventilatory support ; eccentric load-induced injury due to contraction during the expiratory phase ; and longitudinal atrophy caused by high positive end-expiratory pressure. To protect the diaphragm during mechanical ventilation, maintaining proper levels of diaphragm contraction is paramount ; thus, monitoring of respiratory effort and finely tuned ventilator settings are necessary. Furthermore, maintaining of synchronization between the patient and the ventilator is also important. As diaphragm dysfunction is more likely to occur in critically ill patients, diaphragm-protective mechanical ventilation strategies are essential to reduce the mortality rate of intensive care unit patients. This review outlines clinical evidence of ventilator-induced diaphragm dysfunction and its underlying mechanisms, and strategies to facilitate diaphragm-protective mechanical ventilation. J. Med. Invest. 69 : 165-172, August, 2022

Keywords **:** *diaphragm injury, mechanical ventilation, inspiratory effort, atrophy*

INTRODUCTION

In respiratory distressed critically ill patients, it is important to unload respiratory muscles and prevent muscle fatigue and damage, as ventilatory demand significantly exceeds normal respiratory muscle activity (1). Lung injury induced by mechanical ventilation itself and spontaneous breathing effort is well known (2). Moreover, a study reported that mechanical ventilation may also injure the diaphragm (3). In 1988, Knisely *et al*. first reported abnormal thinning of diaphragmatic muscle myofibers in newborns that experienced long-term mechanical ventilation (4). In animal studies, short periods of passive controlled mechanical ventilation (CMV) induced oxidative stress that lead to protein degradation, resulting in diaphragm muscle atrophy and weakness (5-7). In a study with humans, Levine *et al*. (8) reported that prolonged diaphragm inactivity in brain-dead organ donors was associated with marked atrophy of diaphragm myofibers. Since then, rapid diaphragm atrophy and dysfunction under mechanical ventilation were recognized as ventilator-induced diaphragm dysfunction, which is a frequently occurring complication in mechanically ventilated patients (3, 9-12). As diaphragm weakness is present prior to the admission to the intensive care unit (ICU) (13), and sepsis and other critical conditions themselves cause diaphragm fragility (14), the term critical illness-associated diaphragm weakness is also commonly used for diaphragm dysfunction that occurs in the ICU (15).

Preventing diaphragm injury during mechanical ventilation may lead to decreased mechanical ventilator dependence and improved outcome ; thus, it is an important issue for all critical care givers involved in mechanical ventilation. In this review, clinical evidence of ventilator-induced diaphragm dysfunction and its underlying mechanisms, and strategies to facilitate diaphragm-protective mechanical ventilation are outlined.

Received for publication November 29, 2021 ; accepted May 26, 2022.

Address correspondence and reprint requests to Taiga Itagaki M.D., Ph.D., Department of Emergency and Disaster Medicine, Tokushima University Hospital, 2-50-1 Kuramoto-cho, Tokushima, 770-8503, Japan and Fax : +81-88-633-9339. E-mail : taiga@tokushima-u.ac.jp

CLINICAL EVIDENCE

In recent years, it has become possible to evaluate diaphragm function noninvasively at the bedside by ultrasonography (16-18), which has revealed that diaphragm dysfunction is an important issue affecting patient outcomes as well as ICU-acquired weakness. Dres *et al*. (11) evaluated diaphragm function by ultrasonography and examination of twitch tracheal pressure in response to bilateral anterior magnetic phrenic nerve stimulation. In the study, they reported that 63% of mechanically ventilated patients presented diaphragm dysfunction and 21% of patients presented both diaphragm and limb muscle atrophy. Moreover, this diaphragm dysfunction was related to prolonged ICU stay and increased mortality rate. Goligher *et al*. measured the thickening fraction of the diaphragm (TFdi) by ultrasonography, and reported shorter ICU stay in patients with TFdi equivalent to that of healthy subjects at rest (15-30%) (12). Patients that received mechanical ventilation presented with increased and decreased diaphragm thickness, and both conditions were associated with prolonged ventilator dependence and a higher mortality rate.

MECHANISMS OF DIAPHRAGM INJURY INDUCED BY MECHANICAL VENTILATION

To prevent diaphragm dysfunction, it is necessary to understand the mechanisms of diaphragm injury. Atrophy owing to a suppression of inspiratory effort and injury due to an excessive load are the two most important diaphragm injuries during mechanical ventilation. Figure 1 summarizes possible mechanisms of diaphragm injury.

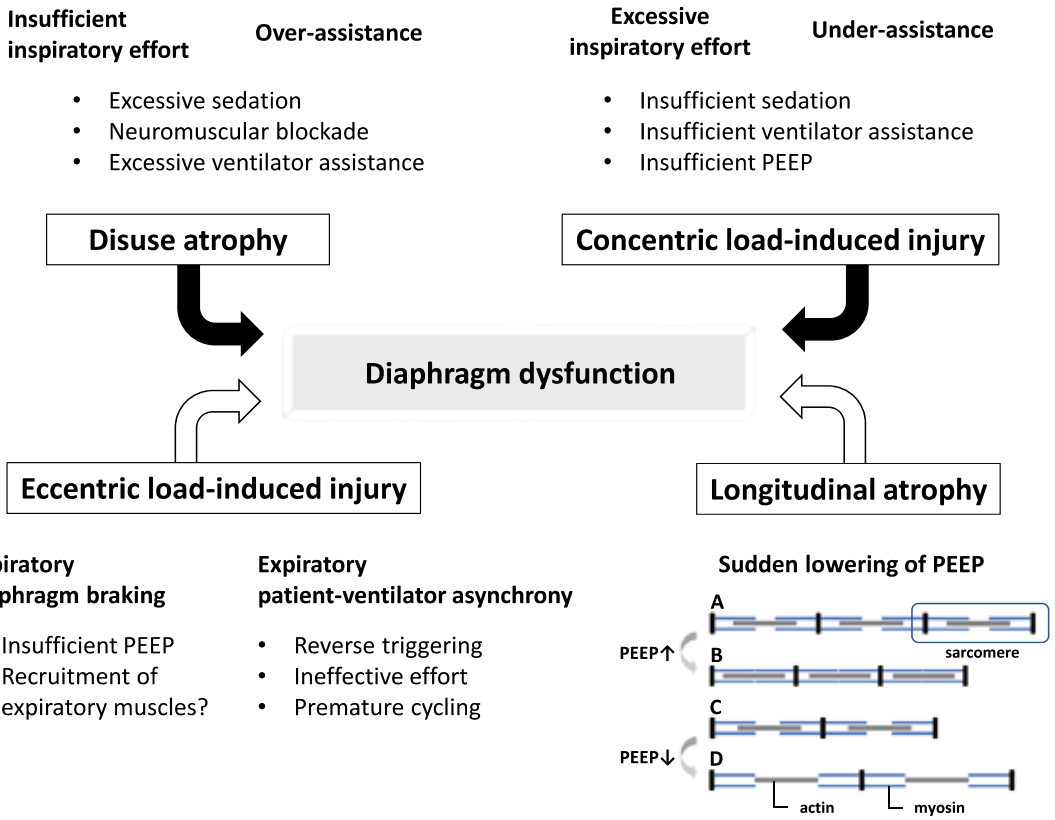

Figure 1. Mechanisms of diaphragm injury induced by mechanical ventilation leading to diaphragm dysfunction. Black arrows indicate mechanisms that have been shown to be associated with poor outcomes. White arrows indicate hypothetical mechanisms based on animal experiments. Lower right schema shows changes in sarcomere length according to changes in PEEP. (A) normal, (B) acute effect of PEEP, (C) long-term effect of persistent high PEEP, and (D) overstretch after the sudden lowering of PEEP.

1. Disuse atrophy

Disuse atrophy due to excessive respiratory support is the most important mechanism of diaphragm injury during mechanical ventilation (19). In animal studies, CMV or high levels of pressure support ventilation caused acute atrophy, damage of myofibers, and dysfunction (5, 20, 21). Levine *et al.* (8) reported that diaphragm inactivity up to 18-69 hours in brain-dead patients was associated with marked atrophy of the diaphragm ; however, it did not cause atrophy in the pectoralis major. Further histological investigations in human subjects revealed that disuse of the diaphragm activated proteolytic pathways and caused both diaphragm atrophy and mitochondrial dysfunction resulting in impaired contractility (22, 23). Previous studies using ultrasonography up to one week after the start of mechanical ventilation or until extubation demonstrated a decrease in end-expiratory thickness of the diaphragm of more than 10% in almost half of mechanically ventilated patients (10, 24). In both studies, decrease in thickness of the diaphragm was observed until the third day of mechanical ventilation, and observed during both controlled and partially assisted ventilation.

2. Concentric load-induced injury

When ventilatory support is insufficient against inspiratory effort, excessive load on the diaphragm causes muscle injury (concentric load-induced injury). In histological examinations in healthy subjects and patients with chronic obstructive pulmonary disease, contraction of the diaphragm against excessive load caused acute (< 90 minutes) diaphragm injury, inflammation, and weakness (25, 26). Importantly, in critically ill patients, especially those with systemic inflammation, sarcolemma is susceptible to mechanical stimuli ; thus, diaphragm dysfunction through this mechanism frequently occurs (27).

3. Eccentric load-induced injury

Muscle injury occurs when muscles eccentrically contract while lengthening (28), and this also applies to the diaphragm (29). Theoretically, this injury may happen in mechanically ventilated patients. One possible cause is patient-ventilator asynchrony (Figure 2). With asynchronies, such as premature cycling, ineffective effort, and reverse triggering, the diaphragm will be forced to contract in the expiratory phase of the ventilator cycle, which results in diaphragm injury (30, 31). Another cause is diaphragm braking. The diaphragm contracts even during expiratory phase and suppresses the rate of decrease in lung volume to prevent acute alveolar collapse and following atelectasis (32, 33). This contraction during the expiratory phase is potentially injurious to the diaphragm (34, 35). Diaphragm braking is strong in situations where alveoli are prone to collapse such as when positive end-expiratory pressure (PEEP) is set low (33). Expiratory muscle contraction may accelerate diaphragm braking. Expiratory muscle recruitment is related to weaning failure especially in patients with small airway obstruction (36, 37). The diaphragm may contract strongly during expiration in cases with recruited expiratory muscles. Further studies are needed.

4. Longitudinal atrophy

When the diaphragm is maintained at a shorter (more caudal)

position with higher PEEP, the sudden lowering of PEEP, such as a spontaneous breathing trial, may cause longitudinal atrophy (38). Although the previous study was an animal study, higher PEEP shortens the length of sarcomeres (the basic contractile unit of muscle fibers composed of two main protein filaments, actin and myosin) in the longitudinal direction, and gradually, some sarcomeres drop out and others regain their original length (reconstruction). Here, the sudden lowering of PEEP causes overstretches of sarcomeres leading to a change in the length-tension relationship of the diaphragm that may cause reduced contraction. Further investigation in human subjects is needed.

CLINICAL STRATEGIES TO FACILITATE DIAPHRAGM-PROTECTIVE MECHANICAL VENTILATION

Preserving spontaneous breathing under light sedation can improve oxygenation and prevent atrophy of respiratory muscles. In recent years, excessive respiratory effort has been shown to exacerbate lung injury, and control of respiratory effort has become recognized as an important element of lung protection (39, 40). However, this lung protective strategy also carries a risk of disuse diaphragm atrophy ; thus, it is important to monitor inspiratory effort and consider how much spontaneous breathing effort should be preserved.

1. Monitoring diaphragm-injurious inspiratory effort

To optimize diaphragm activity for diaphragm protection, adequate monitoring of inspiratory effort is important. For that purpose, direct examination of the diaphragm by ultrasonography is used (Figure 3). Measurement of the diaphragm is performed using B-mode or M-mode ultrasonography with the 10-15 MHz linear transducer perpendicularly placed on the right chest wall at the zone of apposition (41). TFdi is commonly used to quantify diaphragm activity and is calculated as follows : ([thickness at end-inspiration – thickness at end-expiration] / thickness at end-expiration) × 100. TFdi is reported to have a good correlation with transdiaphragmatic pressure (Pdi), direct measurement of pressure generated by the diaphragm and electrical activity of the diaphragm (EAdi) (16).

Esophageal pressure (Pes) is used as a surrogate of pleural pressure (Ppl) to monitor inspiratory effort. To measure Pes, a dedicated esophageal balloon catheter is needed and there are some technical issues about the position of the balloon and the amount of air filled (42). If gastric pressure (Pga) is measured simultaneously, Pdi can be obtained (Pdi = Pga – Pes) (43). EAdi is measured at the gastroesophageal junction by a dedicated catheter fitted with electromyography electrodes and ventilator. EAdi can also precisely monitor inspiratory effort (44). However, EAdi varies widely even in healthy subjects at rest ; thus, it is difficult to specify a target range of EAdi for diaphragm protection (45). Both Pes and EAdi can diagnose patient-ventilator asynchrony when they are monitored with airway pressure and flow waveforms.

$P_{0.1}$ and ΔPocc are simpler methods to evaluate inspiratory effort at the bedside. $P_{0.1}$ is defined as negative deflection of airway pressure when the airway is occluded for 0.1 sec (46, 47). ΔPocc is the airway pressure swing generated by the respiratory muscles when the airway is occluded during a whole breath, and it can estimate respiratory muscle pressure (Pmus) and inspiratory transpulmonary pressure swing (ΔP_L) (48).

Although the cut-off values of safe inspiratory effort that protect the diaphragm are not clear, it is important to maintain diaphragm activity by achieving the inspiratory effort levels of healthy subjects or patients who have been successfully weaned from mechanical ventilation (Table 1) (49, 50).

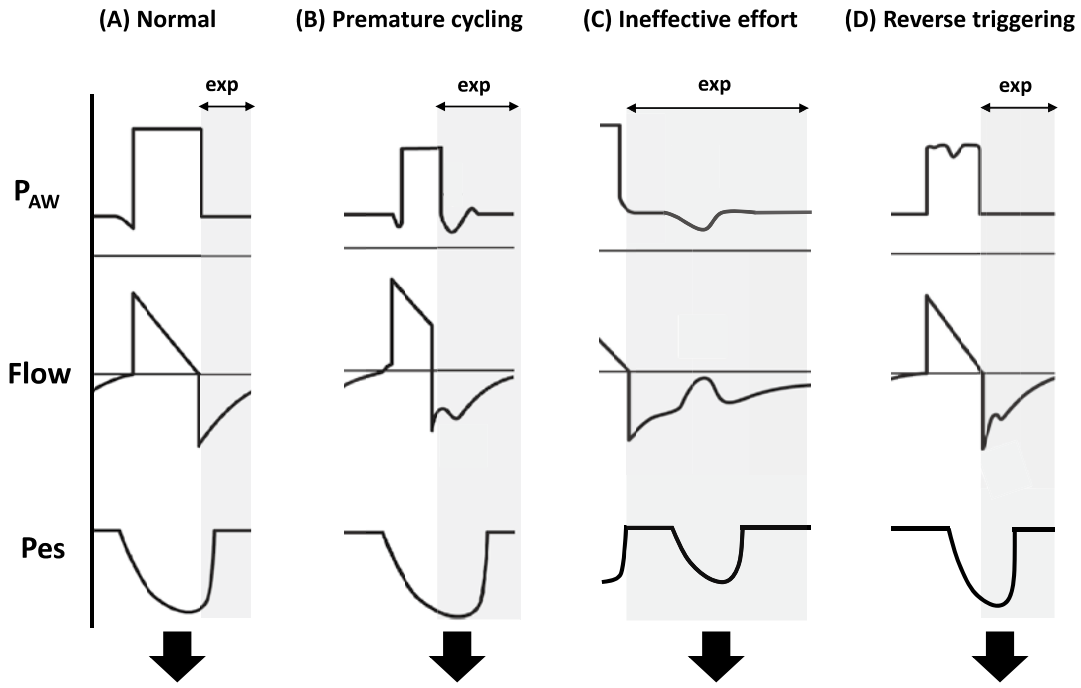

Figure 2. Patient-ventilator asynchronies with eccentric diaphragm contraction.
(A) Normally triggered (synchronous) breath, (B) premature cycling, (C) ineffective effort, and (D) reverse triggering in pressure assist/control ventilation. In A, mechanical insufflation is synchronized with diaphragm contraction. In B to D, negative esophageal pressure swing (black arrow) appears while in the expiratory phase of the ventilator cycle (exp). P_{AW}, airway pressure ; Pes, esophageal pressure.

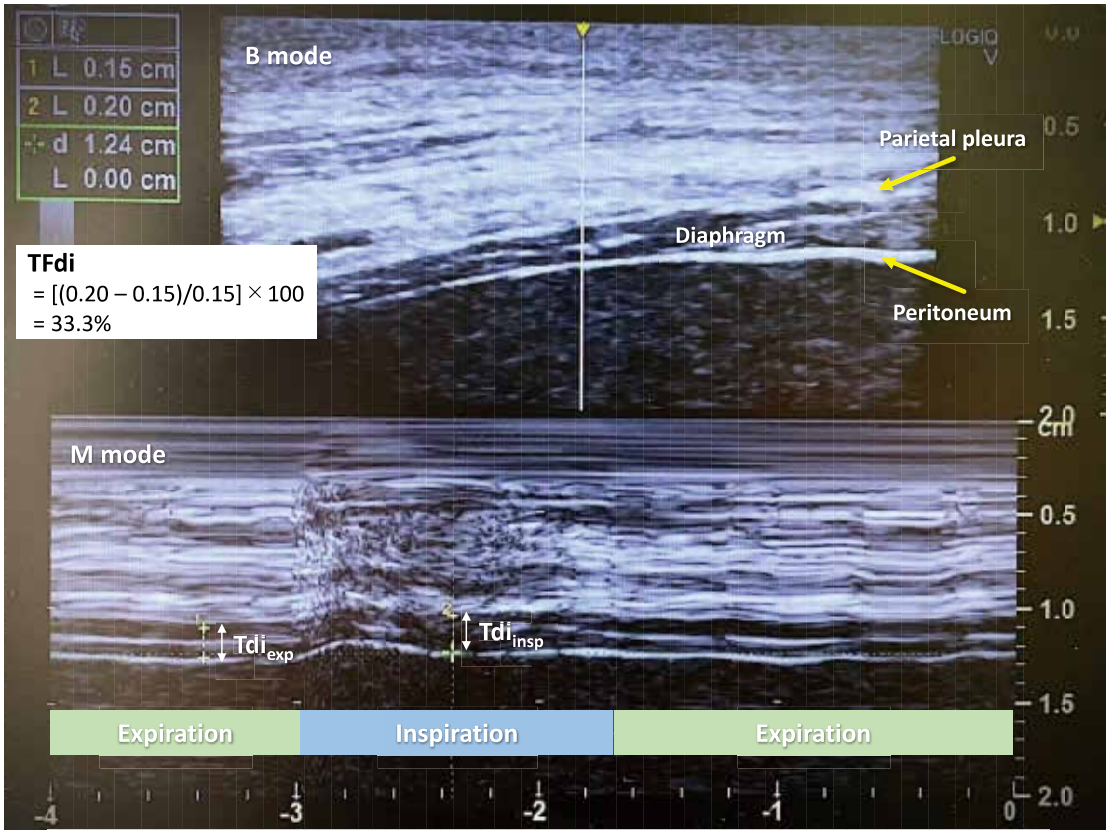

Figure 3. Ultrasonographic assessment of the diaphragm.
The diaphragm is a low-echoic layer sandwiched between parietal pleura and peritoneum with a high-echoic centerline. TFdi, thickening fraction of the diaphragm ; Tdi_{exp}, thickness of the diaphragm at end-expiration ; Tdi_{insp}, thickness of the diaphragm at end-inspiration.

Table 1. Desirable target values of inspiratory effort for diaphragm protection

Parameter	Remarks	Range
Inspiratory thickening fraction of the diaphragm (TFdi)	Diaphragm activity noninvasively assessed by ultrasonography. Continuous monitoring is not feasible.	15-30%
Respiratory muscle pressure (Pmus)	Indicator of pressure generated by inspiratory muscles. Measurement of esophageal pressure is required. Pmus can be estimated from ΔPocc (estimated Pmus=−3/4×ΔPocc).	5-10 cmH_2O
Transdiaphragmatic pressure swing (ΔPdi)	Indicator of pressure generated by the diaphragm. Simultaneous measurements of gastric and esophageal pressure are required.	5-10 cmH_2O
Inspiratory esophageal pressure swing (ΔPes)	Surrogate indicator of inspiratory pleural pressure swing. Direct parameter of inspiratory effort. Placement of esophageal balloon is required.	3-15 cmH_2O
Airway occlusion pressure ($P_{0.1}$)	Negative deflection of P_{AW} when the airway is occluded for 0.1 sec. Simple indicator of inspiratory drive with strong correlation with EAdi and Pmus. Most ICU ventilators can measure this parameter.	1-4 cmH_2O
Airway pressure swing during a whole breath occlusion (ΔPocc)	Airway pressure swing when the airway is occluded during a whole breath. Simple indicator of inspiratory effort. Some ICU ventilators can measure this parameter.	8-20 cmH_2O
Electrical activity of the diaphragm (EAdi)	Diaphragmatic electrical activity measured at gastroesophageal junction. Placement of dedicated catheter fitted with electrodes is required.	Uncertain

P_{AW}, airway pressure.

2. Avoiding inactivity and insufficient unloading of the diaphragm

Ventilator settings

When tidal volume changes by adjusting inspiratory ventilator settings, inspiratory effort will also change (51). This alteration in inspiratory effort is mainly caused by changes in ventilatory demand due to chemoreceptor reflex related to arterial blood pH. If patients are ventilated with excessive tidal volume, inspiratory effort is diminished leading to diaphragm atrophy. On the other hand, insufficient ventilatory support increases the inspiratory effort, resulting in diaphragm injury.

PEEP also affects inspiratory effort (52). Higher PEEP increases end-expiratory lung volume and moves the diaphragm to a more caudal position, which decreases curvature of the diaphragm. From this, neuromechanical coupling will change and pressure generated by the diaphragm decreases. In a previous study, changes in pleural pressure by phrenic nerve stimulation decreased when end-expiratory lung volume was high (53). A recent randomized controlled trial (ROSE trial) (54) examined the effects of an early continuous neuromuscular blocking agent (NMBA) in patients with moderate to severe acute respiratory distress syndrome (ARDS) and found that it did not reduce 90-day mortality contrary to the results observed in a previous randomized controlled trial (55). However, it has been suggested that the higher PEEP strategy applied to the control group (12.5 cmH_2O) may have mitigated inspiratory effort and indirectly protected not only the lungs but also the diaphragm (56). PEEP is hypothesized to have a preventive effect on eccentric load-induced injury as diaphragm braking is suppressed as continuous positive airway pressure levels increase (33). However, caution may be required for longitudinal atrophy potentially caused after sudden lowering of higher PEEP settings.

Mode of mechanical ventilation

The detrimental effects of CMV on the diaphragm can be largely ameliorated by assist-control ventilation (ACV) (57), intermittent spontaneous breathing during CMV (58), pressure support ventilation (59, 60), and adaptive support ventilation (61). Marin-Corral *et al*. (62) reported that Maastricht III organ donors whose diaphragm was stimulated spent 41% of ventilation time in assisted and spontaneous modalities. This resulted in less diaphragm myofiber damage than in brain-dead organ donors relying on full support. Consequently, to preserve spontaneous effort, most critically ill patients who require mechanical ventilation receive assisted and spontaneous modalities (10, 15) ; however, in recent clinical trials, atrophy developed during both controlled and assisted ventilation (10, 12, 16). Itagaki *et al*. reported that the proportion of controlled ventilation during the early-phase of ACV was not associated with maximum variation in diaphragm thickness (63). The mechanism that explains why assisted breaths are diaphragm-protective is unknown (64). Diaphragm atrophy cannot be prevented by the presence of patient triggering, and maintaining optimal inspiratory effort level is more important.

Sedation

Sedation induced by propofol or benzodiazepines reduces respiratory drive and effort, and also alters ventilatory response to hypoxemia and hypercapnea (51, 65). However, for the purpose of regulating excessive inspiratory effort, adjustment of ventilator settings and management of factors increasing respiratory drive, such as metabolic acidosis or pain, should be implemented first before deepening sedation level. Intervention only with sedation did not effectively improve patient-ventilator asynchrony (66, 67).

Neuromuscular blocking agent use

Early NMBA use did not reduce 90-day mortality of ARDS patients in a recent study (54). This result suggests that there are some negative issues in lung protection with NMBA, and diaphragm atrophy is likely to be a factor. Dianti *et al*. (68) conducted a secondary analysis of their prospective cohort study (69) and investigated whether the association between NMBA use and mortality differed according to baseline diaphragm thickness. They found that NMBA was associated with higher mortality in patients with baseline diaphragm thickness $\leq$ 2.3 mm, whereas with lower mortality in patients with baseline diaphragm thickness > 2.3 mm. This result suggests that NMBA may be harmful to patients who already have diaphragm atrophy, and it is important to facilitate lung- and diaphragm-protective ventilation.

3. Managing patient-ventilator asynchrony

Some forms of patient-ventilator asynchrony may cause eccentric contraction of the diaphragm during the expiratory phase, which results in injury. They include reverse triggering, ineffective effort, and premature cycling (30, 31). Thus, maintaining synchronization between spontaneous breathing and assisted ventilation may be diaphragm protective. Monitoring of Pes and EAdi has advantages for diaphragm-protective mechanical ventilation in terms of both detection of asynchronous events and evaluation of inspiratory effort. In our prospective study (70), double triggering on the third day of mechanical ventilation was associated with strong inspiratory effort and may increase diaphragm thickness. Hence, the incidence of double triggering, which is the most lung-injurious asynchrony (71), may function as a surrogate indicator of a diaphragm-injurious breathing pattern.

CONCLUSION

Diaphragm injury during mechanical ventilation is common and associated with increased morbidity and mortality. As excessively weak or strong diaphragm contractions and patient-ventilator asynchrony are the main mechanisms of injury, monitoring and managing respiratory drive and inspiratory effort is important for critical care personnel.

In some cases, especially in severe ARDS, there may be a conflict between lung protection and diaphragm protection as diaphragm inactivity is required to avoid ventilator-induced lung injury or patient self-inflicted lung injury, or both. Although international experts have proposed prioritizing lung protection over protecting the diaphragm when necessary, they prefaced this by stating that every effort should be made to protect both organs simultaneously (35). Further studies are needed to identify personalized target values of respiratory effort to establish lung- and diaphragm-protective ventilation.

CONFLICTS OF INTEREST

This author discloses no conflict of interest.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Heunks L, Ottenheijm C : Diaphragm-protective mechanical ventilation to improve outcomes in ICU patients? Am J Respir Crit Care Med 197(2) : 150-2, 2018
2. Tremblay LN, Slutsky AS : Ventilator-induced lung injury : from the bench to the bedside. Intensive Care Med 32(1) : 24-33, 2006
3. Goligher EC, Brochard LJ, Reid WD, Fan E, Saarela O, Slutsky AS, Kavanagh BP, Rubenfeld GD, Ferguson ND : Diaphragmatic myotrauma : a mediator of prolonged ventilation and poor patient outcomes in acute respiratory failure. Lancet Respir Med 7(1) : 90-8, 2019
4. Knisely AS, Leal SM, Singer DB : Abnormalities of diaphragmatic muscle in neonates with ventilated lungs. J Pediatr 113(6) : 1074-7, 1988
5. Sassoon CS, Caiozzo VJ, Manka A, Sieck GC : Altered diaphragm contractile properties with controlled mechanical ventilation. J Appl Physiol 92(6) : 2585-95, 2002
6. Shanely RA, Zergeroglu MA, Lennon SL, Sugiura T, Yimlamai T, Enns D, Belcastro A, Powers SK : Mechanical ventilation-induced diaphragmatic atrophy is associated with oxidative injury and increased proteolytic activity. Am J Respir Crit Care Med 166(10) : 1369-74, 2002
7. Powers SK, Shanely RA, Coombes JS, Koesterer TJ, McKenzie M, Van Gammeren D, Cicale M, Dodd SL : Mechanical ventilation results in progressive contractile dysfunction in the diaphragm. J Appl Physiol 92(5) : 1851-8, 2002
8. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, Zhu J, Sachdeva R, Sonnad S, Kaiser LR, Rubinstein NA, Powers SK, Shrager JB : Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358(13) : 1327-35, 2008
9. Peñuelas O, Keough E, López-Rodríguez L, Carriedo D, Gonçalves G, Barreiro E, Lorente JÁ : Ventilator-induced diaphragm dysfunction : translational mechanisms lead to therapeutical alternatives in the critically ill. Intensive Care Med Exp 7(Suppl 1) : 48, 2019
10. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, Rittayamai N, Lanys A, Tomlinson G, Singh JM, Bolz SS, Rubenfeld GD, Kavanagh BP, Brochard LJ, Ferguson ND : Evolution of diaphragm thickness during mechanical ventilation : impact of inspiratory effort. Am J Respir Crit Care Med 192(9) : 1080-8, 2015
11. Dres M, Dubé BP, Mayaux J, Delemazure J, Reuter D, Brochard L, Similowski T, Demoule A : Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. Am J Respir Crit Care Med 195(1) : 57-66, 2017
12. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, Vorona S, Sklar MC, Rittayamai N, Lanys A, Murray A, Brace D, Urrea C, Reid WD, Tomlinson G, Slutsky AS, Kavanagh BP, Brochard LJ, Ferguson ND : Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. Am J Respir Crit Care Med 197(2) : 204-13, 2018
13. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, Matecki S, Duguet A, Similowski T, Jaber S : Diaphragm dysfunction on admission to the intensive care unit : Prevalence, risk factors, and prognostic impact - a prospective study. Am J Respir Crit Care Med 188(2) : 213-9, 2013
14. Vassilakopoulos T, Petrof BJ : Ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 169(3) : 336-41, 2004
15. Dres M, Goligher EC, Heunks LMA, Brochard LJ : Critical illness-associated diaphragm weakness. Intensive Care Med 43(10) : 1441-52, 2017
16. Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, Brochard LJ, Bolz SS, Rubenfeld GD, Kavanagh BP, Ferguson ND : Measuring diaphragm thickness with ultrasound in mechanically ventilated patients : feasibility, reproducibility and validity. Intensive Care Med 41(4) : 642-9, 2015
17. Boussuges A, Gole Y, Blanc P : Diaphragmatic motion studied by M-mode ultrasonography. Chest 135(2) : 391-400, 2009
18. Umbrello M, Formenti P, Longhi D, Galimberti A, Piva I, Pezzi A, Mistraletti G, Marini JJ, Iapichino G : Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation : a pilot clinical study. Crit Care 19(1) : 161, 2015
19. Petrof BJ : Diaphragm weakness in the critically ill : basic mechanisms reveal therapeutic opportunities. Chest 154(6) : 1395-403, 2018
20. Yang L, Luo J, Bourdon J, Lin MC, Gottfried SB, Petrof BJ : Controlled mechanical ventilation leads to remodeling of the rat diaphragm. Am J Respir Crit Care Med 166(8) : 1135-40, 2002
21. Radell PJ, Remahl S, Nichols DG, Eriksson LI : Effects of prolonged mechanical ventilation and inactivity on piglet diaphragm function. Intensive Care Med 28(3) : 358-64, 2002
22. Levine S, Biswas C, Dierov J, Barsotti R, Shrager JB, Nguyen T, Sonnad S, Kucharchzuk JC, Kaiser LR, Singhal S, Budak MT : Increased proteolysis, myosin depletion, and atrophic AKT-FOXO signaling in human diaphragm disuse. Am J Respir Crit Care Med 183(4) : 483-90, 2011
23. Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, Bouyabrine H, Courouble P, Koechlin-Ramonatxo C, Sebbane M, Similowski T, Scheuermann V, Mebazaa A, Capdevila X, Mornet D, Mercier J, Lacampagne A, Philips A, Matecki S : Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Am J Respir Crit Care Med 183(3) : 364-71, 2011
24. Nakanishi N, Oto J, Ueno Y, Nakataki E, Itagaki T, Nishimura M : Change in diaphragm and intercostal muscle thickness in mechanically ventilated patients : a prospective observational ultrasonography study. J Intensive Care 7(1) : 56, 2019
25. Orozco-Levi M, Lloreta J, Minguella J, Serrano S, Broquetas JM, Gea J : Injury of the human diaphragm associated with exertion and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164(9) : 1734-9, 2001
26. Jiang TX, Reid WD, Belcastro A, Road JD : Load dependence of secondary diaphragm inflammation and injury after acute inspiratory loading. Am J Respir Crit Care Med 157(1) : 230-6, 1998
27. Lin MC, Ebihara S, El Dwairi Q, Hussain SN, Yang L, Gottfried SB, Comtois A, Petrof BJ : Diaphragm sarcolemmal injury is induced by sepsis and alleviated by nitric oxide synthase inhibition. Am J Respir Crit Care Med 158(5 Pt 1) : 1656-63, 1998
28. Proske U, Morgan DL : Muscle damage from eccentric exercise : mechanism, mechanical signs, adaptation and clinical applications. J Physiol 537(Pt 2) : 333-45, 2001
29. Gea J, Zhu E, Gáldiz JB, Comtois N, Salazkin I, Fiz JA, Grassino A : Functional consequences of eccentric contractions of the diaphragm. Arch Bronconeumol 45(2) : 68-74, 2009

30. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L : Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 32(10) : 1515-22, 2006
31. Akoumianaki E, Lyazidi A, Rey N, Matamis D, Perez-Martinez N, Giraud R, Mancebo J, Brochard L, Richard JM : Mechanical ventilation-induced reverse-triggered breaths : a frequently unrecognized form of neuromechanical coupling. Chest 143(4) : 927-38, 2013
32. Easton PA, Katagiri M, Kieser TM, Platt RS : Postinspiratory activity of costal and crural diaphragm. J Appl Physiol 87(2) : 582-9, 1999
33. Pellegrini M, Hedenstierna G, Roneus A, Segelsjö M, Larsson A, Perchiazzi G : The diaphragm acts as a brake during expiration to prevent lung collapse. Am J Respir Crit Care Med 195(12) : 1608-16, 2017
34. Schepens T, Goligher EC : Lung- and diaphragm-protective ventilation in acute respiratory distress syndrome. Anesthesiology 130(4) : 620-33, 2019
35. Goligher EC, Dres M, Patel BK, Sahetya SK, Beitler JR, Telias I, Yoshida T, Vaporidi K, Grieco DL, Schepens T, Grasselli G, Spadaro S, Dianti J, Amato M, Bellani G, Demoule A, Fan E, Ferguson ND, Georgopoulos D, Guérin C, Khemani RG, Laghi F, Mercat A, Mojoli F, Ottenheijm CAC, Jaber S, Heunks L, Mancebo J, Mauri T, Pesenti A, Brochard L : Lung- and diaphragm-protective ventilation. Am J Respir Crit Care Med 202(7) : 950-61, 2020
36. Volta CA, Dalla Corte F, Ragazzi R, Marangoni E, Fogagnolo A, Scaramuzzo G, Grieco DL, Alvisi V, Rizzuto C, Spadaro S : Expiratory flow limitation in intensive care : prevalence and risk factors. Crit Care 23(1) : 395, 2019
37. Doorduin J, Roesthuis LH, Jansen D, van der Hoeven JG, van Hees HWH, Heunks LMA : Respiratory muscle effort during expiration in successful and failed weaning from mechanical ventilation. Anesthesiology 129(3) : 490-501, 2018
38. Lindqvist J, van den Berg M, van der Pijl R, Hooijman PE, Beishuizen A, Elshof J, de Waard M, Girbes A, Spoelstra-de Man A, Shi ZH, van den Brom C, Bogaards S, Shen S, Strom J, Granzier H, Kole J, Musters RJP, Paul MA, Heunks LMA, Ottenheijm CAC : Positive end-expiratory pressure ventilation induces longitudinal atrophy in diaphragm fibers. Am J Respir Crit Care Med 198(4) : 472-85, 2018
39. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y : The comparison of spontaneous breathing and muscle paralysis in two different severities of experimental lung injury. Crit Care Med 41(2) : 536-45, 2013
40. Yoshida T, Fujino Y, Amato MB, Kavanagh BP : Fifty years of research in ARDS. Spontaneous breathing during mechanical ventilation. Risks, mechanisms, and management. Am J Respir Crit Care Med 195(8) : 985-92, 2017
41. Tuinman PR, Jonkman AH, Dres M, Shi ZH, Goligher EC, Goffi A, de Korte C, Demoule A, Heunks L : Respiratory muscle ultrasonography : methodology, basic and advanced principles and clinical applications in ICU and ED patients - a narrative review. Intensive Care Med 46(4) : 594-605, 2020
42. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, Mojoli F, Chiumello D, Piquilloud L, Grasso S, Jubran A, Laghi F, Magder S, Pesenti A, Loring S, Gattinoni L, Talmor D, Blanch L, Amato M, Chen L, Brochard L, Mancebo J ; PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine) : Esophageal and transpulmonary pressure in the clinical setting : meaning, usefulness and perspectives. Intensive Care Med 42(9) : 1360-73, 2016
43. Shi ZH, Jonkman A, de Vries H, Jansen D, Ottenheijm C, Girbes A, Spoelstra-de Man A, Zhou JX, Brochard L, Heunks L : Expiratory muscle dysfunction in critically ill patients : towards improved understanding. Intensive Care Med 45(8) : 1061-71, 2019
44. Bellani G, Mauri T, Coppadoro A, Grasselli G, Patroniti N, Spadaro S, Sala V, Foti G, Pesenti A : Estimation of patient's inspiratory effort from the electrical activity of the diaphragm. Crit Care Med 41(6) : 1483-91, 2013
45. Bertoni M, Spadaro S, Goligher EC : Monitoring patient respiratory effort during mechanical ventilation : lung and diaphragm-protective ventilation. Crit Care 24(1) : 106, 2020
46. Whitelaw WA, Derenne JP, Milic-Emili J : Occlusion pressure as a measure of respiratory center output in conscious man. Respir Physiol 23(2) : 181-99, 1975
47. Telias I, Junhasavasdikul D, Rittayamai N, Piquilloud L, Chen L, Ferguson ND, Goligher EC, Brochard L : Airway occlusion pressure as an estimate of respiratory drive and inspiratory effort during assisted ventilation. Am J Respir Crit Care Med 201(9) : 1086-98, 2020
48. Bertoni M, Telias I, Urner M, Long M, Del Sorbo L, Fan E, Sinderby C, Beck J, Liu L, Qiu H, Wong J, Slutsky AS, Ferguson ND, Brochard LJ, Goligher EC : A novel non-invasive method to detect excessively high respiratory effort and dynamic transpulmonary driving pressure during mechanical ventilation. Crit Care 23(1) : 346, 2019
49. Jubran A, Grant BJB, Laghi F, Parthasarathy S, Tobin MJ : Weaning prediction esophageal pressure monitoring complements readiness testing. Am J Respir Crit Care Med 171(11) : 1252-9, 2005
50. Goligher EC, Jonkman AH, Dianti J, Vaporidi K, Beitler JR, Patel BK, Yoshida T, Jaber S, Dres M, Mauri T, Bellani G, Demoule A, Brochard L, Heunks L : Clinical strategies for implementing lung and diaphragm-protective ventilation : avoiding insufficient and excessive effort. Intensive Care Med 46(12) : 2314-26, 2020
51. Vaporidi K, Akoumianaki E, Telias I, Goligher EC, Brochard L, Georgopoulos D : Respiratory drive in critically ill patients. Pathophysiology and clinical implications. Am J Respir Crit Care Med 201(1) : 20-32, 2020
52. Morais CCA, Koyama Y, Yoshida T, Plens GM, Gomes S, Lima CAS, Ramos OPS, Pereira SM, Kawaguchi N, Yamamoto H, Uchiyama A, Borges JB, Vidal Melo MF, Tucci MR, Amato MBP, Kavanagh BP, Costa ELV, Fujino Y : High positive end-Expiratory pressure renders spontaneous effort noninjurious. Am J Respir Crit Care Med 197(10) : 1285-96, 2018
53. De Troyer A, Leduc D, Cappello M, Mine B, Gevenois PA, Wilson TA : Mechanisms of the inspiratory action of the diaphragm during isolated contraction. J Appl Physiol 107(6) : 1736-42, 2009
54. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, Gong MN, Grissom CK, Gundel S, Hayden D, Hite RD, Hou PC, Hough CL, Iwashyna TJ, Khan A, Liu KD, Talmor D, Thompson BT, Ulysse CA, Yealy DM, Angus DC : Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 380(21) : 1997-2008, 2019
55. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A ; ACURASYS study investigators : Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 363(12) : 1107-16, 2010

56. Yoshida T, Fujino Y : Monitoring the patient for a safe-assisted ventilation. Curr Opin Crit Care 27(1) : 1-5, 2021
57. Sassoon CS, Zhu E, Caiozzo VJ : Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 170(6) : 626-32, 2004
58. Gayan-Ramirez G, Testelmans D, Maes K, Rácz GZ, Cadot P, Zádor E, Wuytack F, Decramer M : Intermittent spontaneous breathing protects the rat diaphragm from mechanical ventilation effects. Crit Care Med 33(12) : 2804-9, 2005
59. Hudson MB, Smuder AJ, Nelson WB, Wiggs MP, Shimkus KL, Fluckey JD, Szeto HH, Powers SK : Partial support ventilation and mitochondrial-targeted antioxidants protect against ventilator-induced decreases in diaphragm muscle protein synthesis. PLoS One 10(9) : e0137693, 2015
60. Futier E, Constantin JM, Combaret L, Mosoni L, Roszyk L, Sapin V, Attaix D, Jung B, Jaber S, Bazin JE : Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm. Crit Care 12(5) : R116, 2008
61. Jung B, Constantin JM, Rossel N, Le Goff C, Sebbane M, Coisel Y, Chanques G, Futier E, Hugon G, Capdevila X, Petrof B, Matecki S, Jaber S : Adaptive support ventilation prevents ventilator-induced diaphragmatic dysfunction in piglet : an in vivo and in vitro study. Anesthesiology 112(6) : 1435-43, 2010
62. Marin-Corral J, Dot I, Boguña M, Cecchini L, Zapatero A, Gracia MP, Pascual-Guardia S, Vilà C, Castellví A, Pérez-Terán P, Gea J, Masclans JR : Structural differences in the diaphragm of patients following controlled vs assisted and spontaneous mechanical ventilation. Intensive Care Med 45(4) : 488-500, 2019
63. Itagaki T, Nakanishi N, Takashima T, Ueno Y, Tane N, Tsunano Y, Nunomura T, Oto J : Effect of controlled ventilation during assist-control ventilation on diaphragm thickness : a post hoc analysis of an observational study. J Med Invest 67(3.4) : 332-7, 2020
64. Sieck GC, Mantilla CB : Effect of mechanical ventilation on the diaphragm. N Engl J Med 358(13) : 1392-4, 2008
65. Williams K, Hinojosa-Kurtzberg M, Parthasarathy S : Control of breathing during mechanical ventilation : who is the boss? Respir Care 56(2) : 127-36 ; discussion 136-9, 2011
66. de Wit M, Pedram S, Best AM, Epstein SK : Observational study of patient-ventilator asynchrony and relationship to sedation level. J Crit Care 24(1) : 74-80, 2009
67. Chanques G, Kress JP, Pohlman A, Patel S, Poston J, Jaber S, Hall JB : Impact of ventilator adjustment and sedation-analgesia practices on severe asynchrony in patients ventilated in assist-control mode. Crit Care Med 41(9) : 2177-87, 2013
68. Dianti J, Angriman F, Ferreyro BL, Sklar MC, Brochard L, Ferguson ND, Goligher EC : Association of mortality with neuromuscular blockade differs according to baseline diaphragm thickness. Am J Respir Crit Care Med 202(12) : 1717-20, 2020
69. Sklar MC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, Rittayamai N, Harhay MO, Reid WD, Tomlinson G, Rozenberg D, McClelland W, Riegler S, Slutsky AS, Brochard L, Ferguson ND, Goligher EC : Association of low baseline diaphragm muscle mass with prolonged mechanical ventilation and mortality among critically ill adults. JAMA Netw Open 3(2) : e1921520, 2020
70. Itagaki T, Akimoto Y, Nakano Y, Ueno Y, Ishihara M, Tane N, Tsunano Y, Oto J : Relationships between double cycling and inspiratory effort with diaphragm thickness during the early phase of mechanical ventilation : A prospective observational study. PLoS One 17(8) : e0273173, 2022
71. Sousa MLEA, Magrans R, Hayashi FK, Blanch L, Kacmarek RM, Ferreira JC : Clusters of double triggering impact clinical outcomes : insights from the EPIdemiology of Patient-Ventilator aSYNChrony (EPISYNC) cohort study. Crit Care Med 49(9) : 1460-9, 2021